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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/500,911 | 07/08/2004 | Masakuni Noda | 10577.0002-00000 | 7125 |

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FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

| EXAMINER | |
|---|---|
| NGUYEN, QUANG | |
| ART UNIT | PAPER NUMBER |
| 1633 | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/500,911 | NODA ET AL. | |
| | Examiner | Art Unit | |
| | QUANG NGUYEN, Ph.D. | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *2/24/09*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,6 and 12-37* is/are pending in the application.

4a) Of the above claim(s) *12-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/29/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

Applicant's election without traverse of the species tissue factor in the reply filed on 1/29/09 is acknowledged.

Claims 1, 6 and 12-37 are pending in the present application. Claims 12-37 were withdrawn from further consideration because they are directed to non-elected inventions.

Accordingly, claims 1 and 6 are examined on the merits herein with the above elected species.

***Response to Amendment***

All of the rejections in the Office action dated 6/30/08 were withdrawn in light of Applicant's amendment as well as Applicant's arguments of record.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rupprecht et al (Kidney International 51:694-702, 1997; IDS) in view of Einstein (WO 01/04356, IDS), Khachigian (WO 01/30394; IDS), McKay et al (Analytical biochemistry 265:28-34, 1998; Cited previously) and Erlich et al (Am. J. Pathol. 150:873-880, 1997) . ***This is a new ground of rejection.***

Ruprecht et al already demonstrated that Egr-1 induction not only occurs after mitogenic stimulation of mesangial cells (MCs) in culture, but can also be observed with MC proliferation *in vivo* in a rat model of mesangioproliferative glomerulonephritis; and a common reaction pattern of various glomerular kidney diseases such as IgA nephropathy, diabetic nephropathy, membranoproliferative glomerulonephritisis increased proliferation of intrinsic mesangial cells and mesanglial hypercellularity and persistent mesangial hypercellularity together with increased matrix deposition is considered an important factor in progressive glomerular sclerosis and deterioration of renal function (see at least the abstract and page 694). Ruprecht et al also tested the effect of various anti-sense oligonucleotides directed against Egr-1 by comprising comparing the expression of Egr-1 at both mRNA and protein levels in rat glomerular mesangial cells stimulated with PDGF in the presence or absence of antisense

oligonucelotides, and they found that suppression of Egr-1 mRNA and protein induction interfered with MC mitogenesis (see at least page 699, and Figures 4-6).

Ruprecht et al do not teach specifically a method of screening for a therapeutic substance for a renal disease, including diabetic nephropathy (claim 6), wherein said method comprises steps (a)-(g) as recited in independent claim 1.

At the effective filing date of the present application, Einstein (WO 01/04356) already taught at least a screening method for identifying modulators (both inhibitors and/or inducers) of Egr-1 (including human Egr-1) induction since an induction of the transcription factor Egr-1 has been observed to induced in tissues isolated from human heart under conditions of ischemia such as coronary artery disease (see at least Summary of the Invention; page 7, lines 8-10; page 9, lines 3-5; pages 11-15). Einstein also disclosed that Egr-1 usually functions as an activator of target gene transcription for various genes, including platelet derived growth factor B chain genes (page 7, line 25 continues to line 2 of page 8); and Egr-1 recognizes the consensus motif GCG(G/T)GGGCG which is commonly referred to as the GSG motif (page 8, lines 27-28). Einstein further taught that the screening method may utilize any available means of monitoring for changes, including down-regulating expression and activity of Egr-1; and cells or transduced or transfected cell lines would be contacted with agents under appropriate conditions, and the proteins from "agent contacted" cells and control, non-agent contacted cells would be compared for changes in the expression and/or activity of Egr-1 such as the ability of Egr-1 to bind to a GSG consensus containing nucleic acid

molecule (see at least page 14, line 27 continues to line 3 of page 16; and page 17, lines 10-30).

Additionally, Khachigian (WO 01/30394) also taught a screening method for agents which decreases expression, nuclear accumulation and/or activity of Egr-1, including human Egr-1, since Egr-1 is critical in vascular endothelial cell replication and replication and therefor such agents would be useful for cancer treatment via their ability to inhibit angiogenesis (see at least Summary of the Invention; page 15, lines 20-29 and Table 1). Khachigian disclosed that the putative agents may be tested by any suitable means known to those skilled in the art (page 15, lines 20-29). Khachigian further disclosed that Egr-1 binds to the promoters of a spectrum of genes including tissue factor and PDGF-B (page 1, line 34 continues to line 6 of page 2).

Neither the screening methods of Einstein and Khachigian teaches specifically the steps of immobilizing on a solid phase a polynucleotide to which the protein or salt thereof comprising the amino acid sequence of SEQ ID NO:2 (human Egr-1) is capable of binding to and selecting the compound that decreases the level of at least tissue factor (elected species).

However, at the effective filing date of the present application McKay et al already taught an enzyme-linked immunosorbent assay for the detection of agents which interfere with the DNA binding activities of transcription factors exemplified by NF-IL6, wherein the assay involved immobilizing of a target DNA to a solid support and contacting the solid support with a DNA binding transcription factor protein and an antibody that binds specifically to the DNA binding protein; and that this assay may be

readily adapted for robotic manipulation, making it ideal for high through put screening (see at least the abstract; the section entitled "ELISA" and Figure 3). Please note that this assay quantifies both the expression and binding activity of DNA binding transcription factor proteins.

Erlich et al also taught that increased glomerular tissue factor (TF) expression is associated with glomerular fibrin deposition and renal failure in human and experimental crescentic glomerulonephritis, and demonstrated that TF is the major *in vivo* initiator of fibrin deposition in crescentic glomerulonephritis (see at least the abstract).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the teachings of Ruprecht et al. by also establishing a screening method for an agent or a compound that decreases the production of a protein or a salt thereof comprising SEQ ID NO:2 (human Erg-1) and/or decreases the binding activity of the protein or salt thereof (other than the disclosed anti-sense oligonucleotides directed against Egr-1), and the screening method comprises the steps of immobilizing on a solid phase a polynucleotide to which the protein or salt thereof is capable of binding to and selecting the compound that decreases at least tissue factor, including the use of human glomerular mesangial cells in such a screening assay, in light of the teachings of Einstein (WO 01/04356), Khachigian (WO 01/30394), McKay et al and Erlich et al. as discussed above.

An ordinary skilled artisan would have been motivated to carry out the above modifications because: (1) screening methods for identifying inhibitors of Erg-1 expression and/or activity have been successfully taught by both Einstein (WO

01/04356), Khachigian (WO 01/30394) for treating coronary artery disease and cancer, respectively; (2) the enzyme-lined immunosorbent assay of McKay et al would be desirable and selected by an ordinary skilled artisan because it is readily adapted for robotic manipulation and ideal for high through put screening; and (3) an ordinary skilled artisan would select for an agent that decreases the level of tissue factor since Erlich et al already taught at least that increased glomerular tissue factor (TF) expression is associated with glomerular fibrin deposition and renal failure in human and experimental crescentic glomerulonephritis. Additionally, it is further noted that Erg-1 is known to bind to the promoter of tissue factor gene as taught by Khachigian.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Ruprecht et al., Einstein (WO 01/04356), Khachigian (WO 01/30394), McKay et al and Erlich et al., coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

## *Conclusion*

***No claim is allowed.***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

**To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.**

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/QUANG NGUYEN/
Primary Examiner, Art Unit 1633